



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/038,591

01/04/2002

Bruce D. Cohen

ABX-PF2 US

1445

1473

7590

06/22/2004

FISH & NEAVE

1251 AVENUE OF THE AMERICAS

50TH FLOOR

NEW YORK, NY 10020-1105

EXAMINER

HELMS, LARRY RONALD

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/038,591	<b>Applicant(s)</b> COHEN ET AL.	
	<b>Examiner</b> Larry R. Helms	<b>Art Unit</b> 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2004.
- 2a) ☐ This action is **FINAL**.      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-33 is/are pending in the application.
- 4a) Of the above claim(s) 20 and 23-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 15-17 is/are rejected.
- 7) ☒ Claim(s) 7-14, 18, 19, 21 and 22 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>2/7/03</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

1. Applicant's election with traverse of Group I, claims 1-19, 21-22, in Paper filed 4/15/04 is acknowledged. The traversal is on the ground(s) that a search conducted for group I would necessarily be co-extensive with a search for Groups III-V (see page 3 of response). This is not persuasive. As stated in the restriction requirement the product of the antibody can be used in a materially different method in addition to the methods of groups III-V. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.
2. Claims 20, 23-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper filed 4/15/04.
3. Claims 1-19, 21-22 are under examination.

### ***Claim Objections***

4. Claims 7-14, 18-19, 21-22 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend on a multiple dependent claim. See MPEP § 608.01(n). Accordingly, claims 7-14, 18-19, 21-22 have not been further treated on the merits.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 3-6, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 3-4 are indefinite for reciting " $10^{-4}$ " or smaller in claim 3 because there is no unit of measurement associated with the off rate.

B. Claims 5-6 are indefinite for reciting "substantially the same" because it is not clear if the  $K_d$  or the off rate is the same or within what range is contemplated?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 5-6, 15-17 are rejected under 35 U.S.C. ' 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and

readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different  $V_H$  chains (about 50% homologous) can combine with the same  $V_K$  chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different  $V_H$  sequences combine with different  $V_K$  sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, 4.17.3. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. ' 112, first paragraph. See, 37 C.F.R. 1.801-1.809. Applicant's referral to the deposit of the hybridomas on page 74- 75 of the specification is an insufficient assurance that the required deposit has been made and

all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least

Art Unit: 1642

thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

9. Claims 3-4 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated antibody that has the CDR sequence of antibodies 2.12.1 or 2.13.2 or that binds IGF-IR with a  $K_d$  of  $8 \times 10^{-9}$  M, does not reasonably provide enablement for any antibody that has CDR sequences of antibody 2.12.1 or 2.13.2 with no more than 5 conservative substitutions in the CDRs or binds IGF0lr with a  $K_d$  of less than  $8 \times 10^{-9}$  M. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

Art Unit: 1642

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to antibodies which have alterations in the CDRs of the antibodies of 2.12.1 and 2.12.2. The specification teaches the CDR sequences of the 2.12.1 and 2.13.2 and the antibodies have a  $K_d$  of  $8 \times 10^{-9}$  M, but does not enable antibodies as broadly claimed. The scope of the claims is not commensurate with the scope of enablement provided in the specification.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding

Art Unit: 1642

myeloma protein resulted in the loss of antigen-binding function. In addition, Colman (Research in immunology 145:33-36, 1994) teach that example of antigen-antibody interactions paint a confusing picture and a conservative substitution may abolish binding (see page 35). Thus, it is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions or contain conservative substitutions, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Claims 3-4 are broadly drawn to antibodies that bind IGF-IR with  $K_d$  of  $8 \times 10^{-9}$  M or less. While Groves et al (Hybridoma 6:71, 1987) teach antibodies in sheep which have very high affinity, the art does not recognize human antibodies with this high affinity which is encompassed by the claims.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

### ***Claim Rejections - 35 USC § 102***

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

Art Unit: 1642

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Fujita-Yamaguchi (US 2003/0165502, priority to 6/00).

The claims recite a chimeric antibody that binds to human IGF-IR and inhibits binding to IGF-IR and has the properties of claims 3 and 5 binds the same antigen as 2.12.1 antibody.

Fujita-Yamaguchi teach a scFv-FC chimeric antibody that binds human IGF-IR and blocks IGF-I binding and the antibody can inhibit tumor growth (see page 1-2).

Fujita-Yamaguchi is silent as to all of the properties of the antibody and whether they would be those listed in claims 3 and 5. However, it is the Examiner's position that Fujita-Yamaguchi have produced hybridomas which secrete antibodies that are directed to the same antigen that the claimed antibodies bind and have the same properties claimed. One of ordinary skill in the art would reasonably conclude that Fujita-Yamaguchi antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Fujita-Yamaguchi have produced hybridomas that secrete antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody of Fujita-Yamaguchi, the burden of

Art Unit: 1642

proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

### ***Claim Rejections - 35 USC § 103***

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

Art Unit: 1642

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al (US Patent 6,657,103, filed 9/97) and further in view of Rubini et al (Experimental cell research 251:22-32, 1999).

The claims have been described supra and claim 1 recites a human monoclonal antibody.

Kucherlapati et al teach methods to produce human monoclonal antibodies to growth factor receptors that are human antigens (see column 9). Kucherlapati et al does not teach the antigen is IGF-IR. This deficiency is made up for the teachings of Rubini et al.

Rubini et al teach human IGF-IR plays an important role in malignant transformation and antibodies can be used for detection of human cancers (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antigen taught by Rubini et al and produce a human monoclonal antibody as taught by Kucherlapati et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antigen taught by Rubini et al and produce a human monoclonal antibody as taught by Kucherlapati et al because

Art Unit: 1642

Kucherlapati et al teach that growth factor antigens can be used for producing human monoclonal antibodies for in vivo diagnostics and therapy in humans. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antigen taught by Rubini et al and produce a human monoclonal antibody as taught by Kucherlapati et al because Rubini et al teach antibodies to the IGF-IR can be used for diagnostics of human cancers (see abstract). Therefore, it would have been obvious to produce a human monoclonal antibody against IGF-IR for use as a diagnostic or therapeutic in humans because of the advantages taught by Kucherlapati et al of human antibodies and it would have been obvious to produce such because Rubini et al teach why antibodies to IGF-IR would be of use for diagnostics in human cancers.

Kucherlapati et al and Rubini et al is silent as to all of the properties of the antibody and whether they would be those listed in claims 3 and 5. However, it is the Examiner's position that the antibody produced in view of Kucherlapati et al and Rubini et al would have the recited properties because the antibodies are directed to the same antigen that the claimed antibodies bind and would obviously have the same properties claimed. One of ordinary skill in the art would reasonably conclude that the antibody produced in view of Kucherlapati et al and Rubini et al also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that the antibody produced in view of Kucherlapati et al and Rubini et al have produced hybridomas that secrete antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and

Art Unit: 1642

comparing the claimed antibody with the antibody produced in view of Kucherlapati et al and Rubini et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubini et al (Experimental cell research 251:22-32, 1999) and further in view of Adair et al (WO 91/09967, published 7/91).

The claims have been described supra and claim 1 recites a humanized monoclonal antibody.

Rubini et al teach a monoclonal antibody to human IGF-IR and the antibody inhibits IGF-I binding and does not cross-react with insulin receptor and the antibody recognizes autophosphorylation of IGF-IR (see entire document). Rubini et al does not teach a humanized antibody. This deficiency is made up for the teachings of Adair et al.

Adair et al teach methods to humanize antibodies and the advantages of such (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have humanized the antibody of Rubini et al by the method of Adair et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have humanized the antibody of Rubini et al by the method of Adair et al because Rubini et al teach antibodies to the IGF-IR can be used for diagnostics of human cancers (see abstract). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have humanized the antibody of Rubini et al by the method of Adair et al because Adair et al teach humanization methods that have worked on many antibodies and the humanization method is performed to produce an antibody that has a reduced HAMA response in humans. Therefore, it would have been obvious to produce a humanized monoclonal antibody against IGF-IR for use as a diagnostic or therapeutic in humans because of the advantages taught by Adair et al of humanized antibodies and it would have been obvious to produce such because Rubini et al teach why antibodies to IGF-IR would be of use for diagnostics in human cancers and it would have been obvious to humanize the antibody of Rubini et al for therapy in humans to reduce the HAMA response as taught by Adair et al.

Adair et al and Rubini et al is silent as to all of the properties of the antibody and whether they would be those listed in claims 3 and 5. However, it is the Examiner's position that the antibody produced in view of Adair et al and Rubini et al would have the recited properties because the antibodies are directed to the same antigen that the claimed antibodies bind and would obviously have the same properties claimed. One of ordinary skill in the art would reasonably conclude that the antibody produced in view of Adair et al and Rubini et al also possesses the same structural and functional

properties as those of the antibodies claimed and, therefore, it appears that the antibody produced in view of Adair et al and Rubini et al have produced hybridomas that secrete antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody with the antibody produced in view of Adair et al and Rubini et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Conclusion***

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by

Art Unit: 1642

CHRISTINA CHART  
telephone are unsuccessful, the examiner's supervisor, ~~Yvonne Eyle~~, can be reached  
at (571) 272-087<sup>41</sup>~~4~~.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832



LARRY R. HELMS, PH.D.  
PRIMARY EXAMINER